REMARKS/ARGUMENTS

Reconsideration of this patent application is respectfully requested in view of the foregoing amendments, and the following remarks.

The foregoing amendments and following remarks supplement the amendments and remarks presented in Applicants' Amendment in Response to Final Office Action which was filed on January 9, 2008. Consideration of the January 9, 2008 Amendment After Final was requested in a Request for Continued Examination filed on February 6, 2008 and entry of same is presumed.

The claims are 1, 2 and 4-24. Claims 1, 2, 13 and 14 have been amended to more clearly define the invention. In particular, claims 1, 2, 13 and 14 have been amended to recite that the inflow function i(t) is iteratively determined *from said non-pulsatile component*. Support for the amendments to claims 1, 2, 13 and 14 may be found, *inter alia*, in the disclosure as filed at page 11, last paragraph and in FIG. 2. No new matter has been introduced.

New independent claim 24, which incorporates the subject
matter of independent claim 2 as amended, and dependent claim 3,
has been added. Dependent claim 3 has been cancelled without
prejudice.

Claims 1, 2, 4, 7-9, 11-16 and 19-20 were rejected under 35
U.S.C. 103(a) as being unpatentable over *U.S. Patent No.
6,223,069 to Pfeiffer et al.,* in view of U.S. Patent No.
6,339,714 to *Chen*. The remaining claims 3, 5, 6, 10, 17, 18 and
21-23 were rejected under 35 U.S.C. 103(a) as being unpatentable
over *Pfeiffer et al* and *Chen* and further in view of *U.S. Patent
No. 6,516,214 to Boas.*

Essentially the Examiner's position was that *Pfeiffer et al.*
discloses the device for measuring cerebral blood flow in an
organ using an injected indicator recited in the claims except
for delineating that the signal is divided into pulsatile and
nonpulsatile components, that *Chen* discloses this feature, and
that it would have been obvious to one of ordinary skill in the
art at the time the invention was made to incorporate this
feature into *Pfeiffer et al.* for the purpose of obtaining the
attenuation purely due to arterial blood. *Boas* was cited with

respect to claims 3, 5, 6, 10, 17, 18 and 21-23 as teaching the use of a threshold value for comparison purposes and extrapolation of data for determining location.

The rejections are respectfully traversed.

As set forth in amended independent claims 1 and 13, Applicants' invention provides a device and a method, respectively, for measuring blood flow in an organ using an injected indicator. As recited in amended claim 1, the device includes a radiation source for emitting near infrared radiation into tissue of the organ at a first location, a sensor for detecting a proportion of the emitted near infrared radiation that exits from the organ at a second location, and an evaluation unit that detects the proportion of the emitted near infrared radiation that exits from tissue of the organ as an input signal. The input signal contains a pulsatile component and a non-pulsatile component, and the evaluation unit is programmed to perform the following evaluation steps:

(a) dividing up the input signal into the pulsatile component and the non-pulsatile component;

(b) determination of injected indicator concentration with

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reference to the organ tissue from the non-pulsatile component of the input signal;

(c) iterative determination, from the non-pulsatile component, of an inflow function i(t) that characterizes blood flow through the organ by incrementally varying a mean transit time mtt until a stop criterion is reached;

(d) determination of injected indicator concentration with reference to blood volume in the organ from the pulsatile component of the input signal and the iteratively determined inflow function i(t);

(e) calculation of blood volume in the organ as a quotient of the injected indicator concentration with reference to the organ tissue and the injected indicator concentration with reference to the blood volume in the organ; and

(f) calculation of the blood flow in the organ as a quotient of the blood volume in the organ and the mean transit time mtt when the stop criterion has been reached.

These steps (a)-(f) are also recited in amended method claim

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13.

Amended independent claims 2 and 14 incorporate the subject matter of amended claims 1 and 13, respectively, and further recite scaling the inflow function i(t) by means of values determined from the pulsatile component of the input signal.

New independent claim 24 incorporates the subject matter of claim 2 as amended and further recites the subject matter of cancelled claim 3, in particular back-extrapolation of the scaled inflow function i(t) to a time of injection of the indicator.

None of the cited references discloses or suggests the device and method as recited in the pending claims. The references also fail to achieve the benefits that result from the device and method as recited in Applicants' claims.

Pfeiffer et al. (US 6,223,069) discloses a process and device for non-invasive measurement of cerebral blood flow and determination of a blood flow index and a relative blood volume (See *Pfeiffer et al.* at column 8, lines 13-15). In order to accomplish these objectives with the method and device according

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to *Pfeiffer et al.*, it is <u>necessary</u> to **measure two functions**

$(a(t)$ and $c(t))$, to evaluate the transcerebral transport function

$(g(t))$ from the **two** measured functions and to determine the blood

flow index by way of specific values of the evaluated
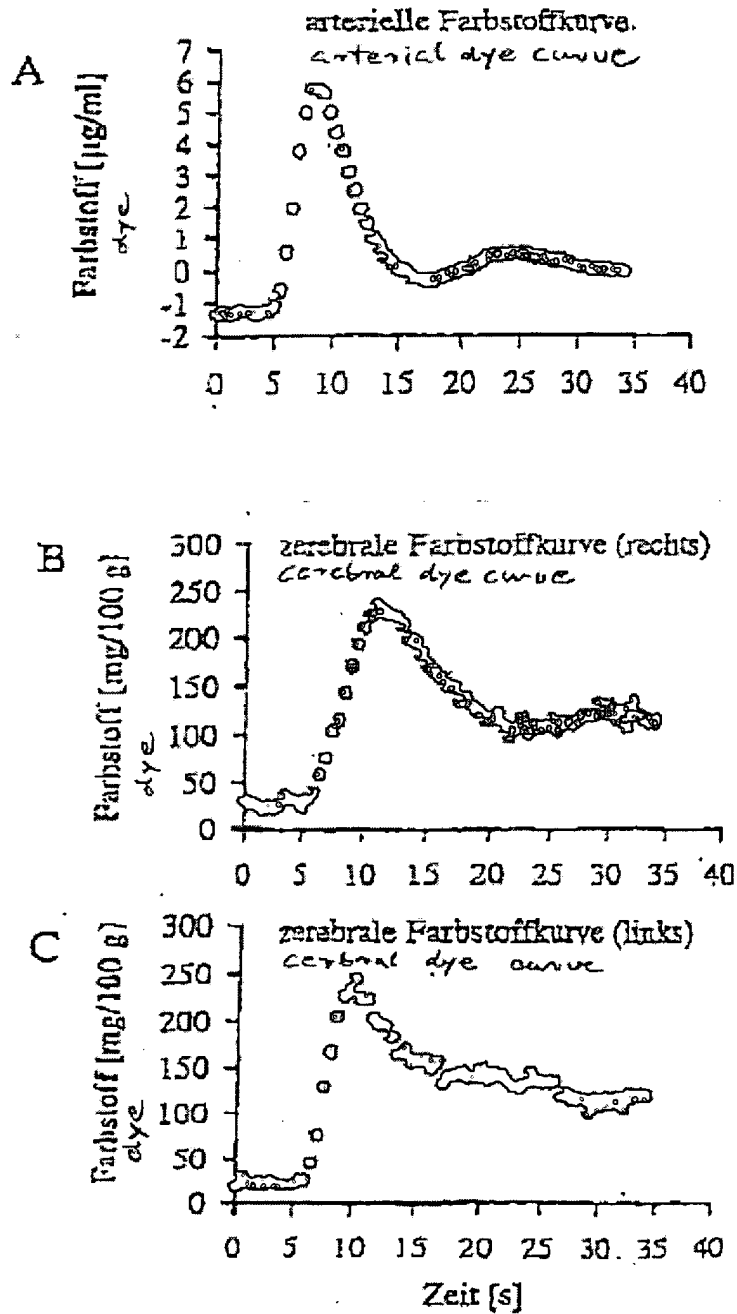
transcerebral transport function $(g(t))$.

In studying the cited *Pfeiffer et al.* reference, Applicants

have become aware of a number of inconsistencies between the

specification, in particular at column 7, lines 11-33, and the

drawing figures of *Pfeiffer et al.* For example, the values for

t_x and t_y indicated at column 7, line 26 of *Pfeiffer et al.* (2.40

s and 5.58 s, respectively) do not correspond with the values

indicated in FIGS. 2 or 3. Additionally, the signal values and

their units (ml/100 g) indicated at column 7, lines 17 and 23-24

of *Pfeiffer et al.* do not correspond with the signal values and

units indicated in FIGS. 2 or 3.

It appears that these errors in the cited *Pfeiffer et al.*

reference are the result of the wrong drawing figures being filed

in the PCT application which issued as *Pfeiffer et al.*

Applicants believe that the correct drawing figures may be found

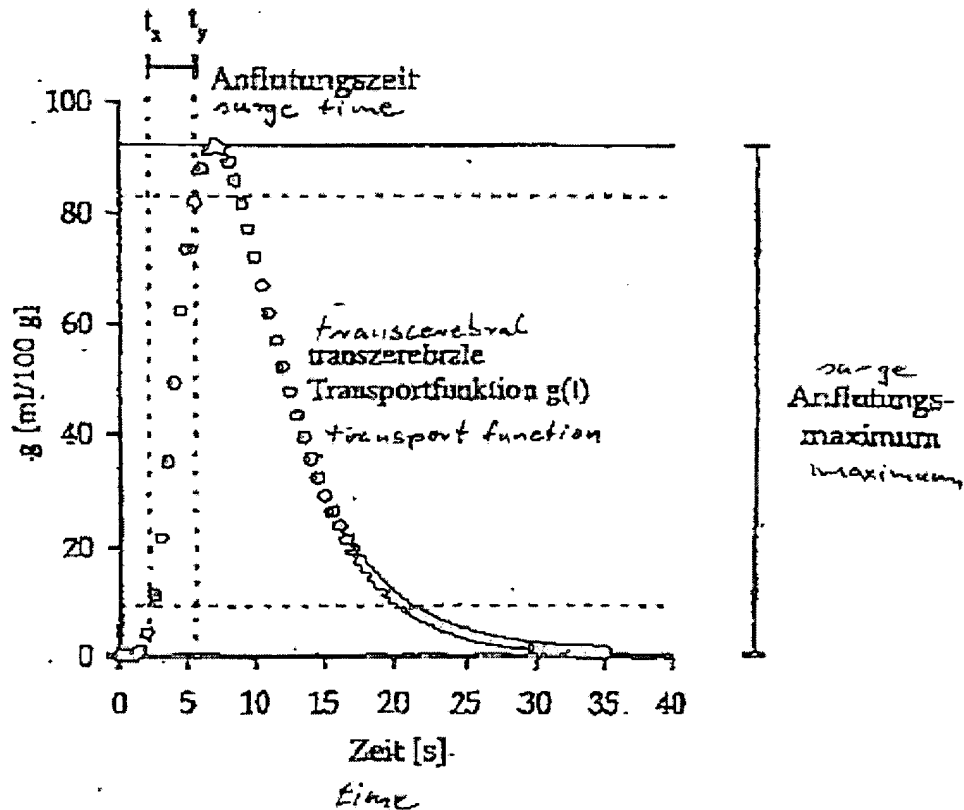in the annex to the International Preliminary Patentability

Report for PCT application PCT/EP97/04725 and in corresponding

European Patent Application EP 0 928 156 (EP '156). In

particular, Applicants have studied EP '156 which is based on the

same PCT Application (PCT/EP97/04725) as the cited *Pfeiffer et*

al. reference and believe that FIGS. 2 and 3 of EP '156

correspond to the discussion in the *Pfeiffer et al.* reference as

set forth above. A copy of the EP '156 reference is enclosed

with the Second Supplemental Information Disclosure Statement

accompanying this Amendment.

As the correct drawings of EP '156 may aid in understanding

the teachings of *Pfeiffer et al.*, reproduced below are FIGS. 2A, B

and C and FIG. 3 of EP '156, which figures have been annotated

with an English language translation of the text.

Figur 2

A — arterielle Farbstoffkurve. / arterial dye curve

B — zerebrale Farbstoffkurve (rechts) / cerebral dye curve

C — zerebrale Farbstoffkurve (links) / cerebral dye curve

Zeit [s]

Figur 3

In particular, FIGS. 2 and 3 of *Pfeiffer et al.* correspond to FIG. 2A and 2b of EP -156, reproduced above, with additional but technically meaningless marks for t_x and t_y. Moreover, the values given in column 7, lines 11-33 of *Pfeiffer et al.* are consistent with FIG. 3 of EP '156 and not with any of the figures included in *Pfeiffer et al.*

In conclusion, Applicants submit that the determination of g(t) from two measurements as required in *Pfeiffer et al.* and shown in FIGS. 2A and B or 2B and C of EP '156 and the determination of blood flow index and blood volume from specific values of g(t) as required in *Pfeiffer et al.* and shown in FIG. 3 of EP '156 is more easily understood when the description of *Pfeiffer et al.* is considered in conjunction with the relevant corresponding drawing figures.

As recited in amended claim 1, Applicants' invention relates to a device for measuring blood flow in an organ. The proportion of emitted near infrared light is detected as an input signal and an injected indicator concentration is determined from this input signal. Furthermore, an inflow function i(t) that characterizes blood flow thorough the organ is determined from the input signal by incrementally varying a mean transmit time (mtt) until a stop criterion is reached. Inflow function i(t) is neither directly measured nor determined from two measurement. Thus, the inflow function i(t) as recited Applicants' claims is substantially different with regard to all functions disclosed in *Pfeiffer et al.*

Moreover, as recited in Applicants' claims, the injected indicator concentration is determined with reference to the blood volume **in the organ** from the detected input signal and the inflow function i(t), which inflow function i(t) is also determined from the detected input signal. None of the references cited by the Examiner disclose or suggest such an evaluation step.

As recited in Applicants' claims, the blood volume in the organ is calculated as a quotient of the injected indicator concentration with reference to the organ tissue and the injected indicator concentration with reference to the blood volume in the organ. Thus the blood volume in the organ is also determined from the detected input signal. Finally, the blood flow in the organ is calculated as a quotient of the blood volume in the organ and the mean transit time (mtt) when the stop criterion is reached. Since the two latter values are also determined from the detected input signal, the blood flow in the organ is also determined from the detected input signal.

The Examiner has indicated in the January 23, 2008 Advisory Action that Applicants' claims do not particularly specify a single signal and absolute values. However, in Applicants'

pending claims, only an input signal is defined and all other values are determined from said/the input signal. Thus, Applicants respectfully submit that the pending claims recite that all values are determined and calculated from said **detected input signal**, i.e. a single input signal and not from two measured signals as disclosed in *Pfeiffer et al.* and *Chen*. There is no disclosure in Applicants' description of a second input signal, because no second input signal is required in the device and method recited in Applicants' claims.

That the values recited in Applicants' claims are absolute values is implicit, because the determined values all refer to the organ blood volume or organ tissue. This feature provides for the determination of absolute values.

The device and method according to Applicants' pending claims achieves substantial benefits, which cannot be achieved by the subject matter disclosed in the cited references. In particular, with the devices and methods taught by *Pfeiffer et al., Chen* and *Boas*, it is simply not possible to get the desired results from single signal or to obtain absolute values. These substantial benefits are achieved with Applicants' invention as

recited in the pending claims.

Moreover, the evaluation steps recited in Applicants' claims result in a substantially different and beneficial way of determining cerebral blood volume and blood flow. According to Applicants' claims, cerebral blood volume is determined <u>before</u> cerebral blood flow. In particular, as recited claim 1, blood flow in the organ is calculated "*as a quotient of blood volume in the organ and the mean transit time mtt when the stop criterion has been reached.*" It is not possible to determine cerebral blood volume before the cerebral blood flow in the references cited by the Examiner. Thus, the subject matter of Applicants' claims are believed to be novel and inventive over the cited references. Moreover, the novel evaluation steps recited in Applicants' claims cannot be deduced from a combination of the cited references, as the evaluation steps recited in Applicants' claims are neither disclosed nor suggested in any of the cited references.

In particular the cited *Pfeiffer et al.* patent fails to teach or suggest at least the following features recited in Applicants' claims:

o dividing a detected input signal into pulsatile and
   non-pulsatile components;

o determining the injected indicator concentration with
   reference to the organ tissue from the detected input
   signal, specifically from detected the input signal's
   non-pulsatile component;

o iteratively determining an inflow function from the
   input signal by incrementally varying a mean transit
   time;

o determining the injected indicator concentration with
   reference to blood volume **in the organ** from the input
   signal, specifically from the pulsatile component of
   the input signal **and** the iteratively determined inflow
   function

o calculating a blood volume **in the organ** as a quotient
   of the injected indicator concentration with **reference
   to the organ tissue** and the injected indicator
   concentration with reference to the blood volume **in the
   organ**;

o calculating the blood flow in the organ as a quotient
   of the blood volume in the organ and the mean transit
   time (mtt) when a stop criterion is reached.

The defects and deficiencies of the primary reference to

Pfeiffer et al. are nowhere remedied by the secondary references

to *Chen* and *Boas*.

In particular, *Chen* teaches the division of an input signal

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into a pulsatile and non-pulsatile component. However, *Chen*

fails to teach or suggest at least the following features recited

in Applicants' claims:

- o determining the injected indicator concentration from
     the detected input signal, specifically from the
     detected input signal's non-pulsatile component;

- o iteratively determining an inflow function from the
     input signal by incrementally varying a mean transit
     time;

- o determining the injected indicator concentration with
     reference to blood volume **in the organ** from the input
     signal, specifically from the pulsatile component of
     the input signal **and** the iteratively determined inflow
     function

- o calculating a blood volume **in the organ** as a quotient
     of the injected indicator concentration with **reference
     to the organ tissue** and the injected indicator
     concentration with reference to the blood volume **in the
     organ**;

Applicants' independent claims 2 and 14 recite the subject

matter of amended claims 1 and 13, respectively, and further

recite scaling the inflow function i(t) by means of values

determined from the pulsatile component of the input signal.

None of the references cited by the Examiner relate to the

scaling of a function as recited in claims 2 and 14. For this

reason, as well as for the reasons set forth above, it is believed

that claims 2 and 14 are allowable over the cited references, either along or in combination.

New independent claim 24 incorporates the subject matter of claim 2 as amended and further recites the subject matter of cancelled claim 3, in particular back-extrapolation of the scaled inflow function i(t) to a time of injection of the indicator. This feature is also recited in Applicants' dependent claim 15.

The Examiner has taken the position that the subject matter of former claim 3 is obvious over *Pfeiffer et al.* and *Chen* and further in view of *Boas*. As the Examiner noted in the Office Action dated October 9, 2008, *Boas* shows an extrapolation of data for determining a **location**. The Examiner has not explained, however, how an extrapolation of data for determining a **location** would make obvious a back-extrapolation of a scaled inflow function i(t) to a **time** of injection of the indicator as claimed in Applicants' pending claims 24 and 15. The back extrapolation as recited in Applicants' claims corresponds to a back extrapolation of a chronological run of a function in a not measured past. This feature is substantially different from the extrapolation of data for determining a **location**, as taught by

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Boas. The only common ground between the teaching of *Boas* and Applicants' claims 15 and 24 is the word "extrapolation", which word can be found in any basic graduate math text. This does not make obvious all kinds of extrapolations. None of the cited references would give a person of ordinary skill in the art any suggestion to use a back-extrapolation of an input signal to a time of injection, as recited in Applicants' claims 15 and 24.

An additional benefit from the back-extrapolation as recited in Applicants' claims is that the amount of the indicator administered to the patent does not need to be known. This benefit is not achieved in the cited references (see for example claim 1 of *Pfeiffer et al.*, which recites "*intravenously administering a predetermined amount of a tracer substance*").

Moreover, *Boas* fails to teach or suggest at least the following features recited in Applicants' claims:

- dividing a detected input signal into pulsatile and non-pulsatile components;

- determining the injected indicator concentration from the detected input signal, specifically from detected the input signal's non-pulsatile component;

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- iteratively determining an inflow function from the input signal by incrementally varying a mean transit time;

- determining the injected indicator concentration with reference to blood volume **in the organ** from the input signal, specifically from the pulsatile component of the input signal **and** the iteratively determined inflow function

- calculating a blood volume **in the organ** as a quotient of the injected indicator concentration with **reference to the organ tissue** and the injected indicator concentration with reference to the blood volume **in the organ**;

- **back-extrapolating** the scaled inflow function to a **time** of injection of the indicator.

For the reason set forth above, Applicant believes the claims, which are 1, 2 and 4-24, are allowable over the cited references, considered alone or in combination.
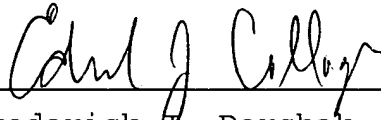
This Application as amended includes five (5) independent claims, claims 1, 2, 13, 14 and 24. Authorization to charge the undersigned's Deposit Account Number 03-2568 for payment of the official fee for one (1) independent claim in excess of three (3) was given in the previous Amendment filed on January 9, 2008.

The Commissioner is hereby authorized to charge the undersigned's Deposit Account No. 03-2468 in the amount of $210.00 representing the official fee for one (1) additional independent claim in excess of three (3) in the application.

In summary, claims 1, 2, 13 and 14 have been amended. New claim 24 has been added and claim 3 has been cancelled without prejudice. In view of the foregoing, it is respectfully requested that the claims be allowed and that this application be passed to issue.

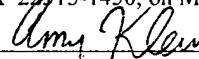Respectfully submitted,
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enclosures: Second Supplemental Information Disclosure
               Statement with Form PTO-1449 and one (1) reference

I hereby certify that this correspondence is being deposited with the U.S. Postal Service as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on March 13, 2008.

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Amy Klein

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